Exploring the link between anabolic-androgenic steroids abuse for performance improvement and hepatocellular carcinoma: a literature review

Explorando a relação entre hepatocarcinoma e o abuso de esteroides anabolizantes para otimização da aptidão física: uma revisão de literatura

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ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) corresponds to 90% of primary malignant liver cell carcinomas and is a leading cause of cancer-related death worldwide. **Objective:** This compilation of cases aimed to identify evidence of correlation between anabolic androgen steroids (AAS) abuse for performance improvement by healthy subjects and HCC. **Methods:** We performed a literature review and identified 935, 1148, 12 and 3 articles in Pubmed, Embase, Scopus and Lilacs, respectively. Only studies, reviews and case reports evaluating the association between androgens and hepatocarcinoma were included with no restrictions in time span or language. Further on, we excluded studies and case reports which patients were receiving therapeutic androgens and collected data only of those reporting androgen intake to improve physical performance. **Results:** Six articles fulfilled the inclusion criteria, excluding the duplicates. HCC onset after AAS abuse seems to occur at earlier ages than those related to chronic hepatitis B/C, chronic alcohol consumption and nonalcoholic steatohepatitis (NASH). Timeframe ranged from two to seven years in the cases reports presented here. Many AAS subtypes were used by patients depicted in the case reports, so it is difficult to conclude if a specific AAS is safer or more harmful than the other. Carcinogenic mechanisms are poorly understood, but pre-clinical evidence shows that androgen receptors and oxidative stress may play a pivotal role in its development. **Conclusion:** The evidence that HCC has been linked to long term AAS abuse for performance improvement is scant but some association is suggested. AAS must be taken only under specialized supervision and the putative correlation with HCC calls for public policies to make high risk populations aware of the risks of misuse and self-administration.

Keywords: Hepatocellular carcinoma; Anabolic androgen steroids; Testosterone congeners

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RESUMO

Introdução: O hepatocarcinoma (HC) corresponde a 90% das neoplasias malignas primárias do fígado, sendo uma importante causa de morte relacionada a neoplasias no mundo. **Objetivo:** Esta compilação de casos tem como intenção identificar uma possível correlação entre hepatocarcinoma e o abuso de esteroides anabolizantes (EA) para otimização da aptidão física em indivíduos saudáveis. **Métodos:** Foi realizada uma revisão de literatura na qual se identificaram 935, 1148, 12 e 3 artigos no Pubmed, Embase, Scopus e Lilacs, respectivamente. Foram incluídos, inicialmente, apenas estudos clínicos, revisões de literatura e relatos de caso avaliando a associação entre EA e HC, sem restrições quanto ao período e linguagem. Excluíram-se os estudos clínicos e os relatos de caso nos quais os pacientes receberam EA com objetivo terapêutico, sendo, portanto, coletados dados apenas dos artigos reportando o uso de EA para melhora da aptidão física. **Resultados:** Seis artigos preencheram os critérios de inclusão, excluindo-se as duplicações. O surgimento de HC após abuso de EA parece ocorrer em idades mais precoces quando se compara com o HC relacionado aos vírus da hepatite B e C, consumo crônico de álcool e esteato-hepatite não alcoólica (NASH). O intervalo para surgimento da neoplasia a partir do início do abuso de EA variou entre 2 a 7 anos nos relatos de caso descritos nesta revisão. Diversos tipos de EA foram utilizados pelos pacientes descritos nos relatos de caso, o que torna difícil qualquer conclusão sobre qual EA teria um maior perfil de segurança ou risco. Os mecanismos de carcinogênese são pouco conhecidos, mas evidências pré-clínicas sugerem que os androgênios e o estresse oxidativo podem estar diretamente relacionados ao desenvolvimento de HC. **Conclusão:** As evidências relacionando HC e o abuso de EA para otimização da aptidão física são escassas, contudo os dados presentes da literatura sugerem que algum grau de associação é possível. EA devem ser utilizados apenas sob supervisão especializada e a possibilidade de haver uma associação com HC reforça a necessidade de políticas públicas para alertar às populações de maior risco sobre os perigos do uso incorreto e sem supervisão de esteroides anabolizantes.

Descritores: Carcinoma hepatocelular; Esteroides andrógenos anabólicos; Congêneres da testosterona

INTRODUCTION

Hepatocellular carcinoma (HCC) corresponds to 90% of primary malignant liver cell carcinomas and is a leading cause of cancer-related death worldwide. The prevalence of HCC is higher in males than in females (2.4:1), as well the incidence in Eastern and Southern Asia, Middle and Western Africa, Melanesia and Micronesia/Polynesia.^(1,2)

Many different etiological factors are involved in the development of HCC as chronic hepatitis B/C, chronic alcohol consumption, nonalcoholic steatohepatitis (NASH) and aflatoxin exposure.⁽¹⁻³⁾ Less common factors are long-term use of oral contraceptives and high-dose anabolic androgenic steroids.^(1,3)

The association between androgen exposure and the development of HCC was first reported by Recant and Lacy in 1965 in a male patient with Fanconi's Anemia. Since this publication, several clinical reports have been published linking long term androgen exposure to HCC in Fanconi's and non-Fanconi's patients.^(4,5)

Anabolic androgen steroids (AAS), synthetically produced hormones analogs to male testosterone, are commonly misused and self-administrated by healthy subjects to enhance physical performance. This independent practice raises concerns because the majority of users are not aware of their potential life threatening risks.^(6,7)

This compilation of published case reports aims to identify evidence linking anabolic-androgen steroids

abuse for physical performance improvement in healthy subjects and hepatocellular carcinoma.

METHODS

We performed a literature review searching in PubMed, Embase, Scopus and Lilacs databases using the following key words: 'liver cell carcinoma'/exp OR 'carcinoma, hepatic cell' OR 'carcinoma, hepatocellular' OR 'carcinoma, liver' OR 'carcinoma, liver cell' OR 'hepatic carcinoma' OR 'hepatic cell carcinoma' OR 'hepatocarcinoma' OR 'hepatocellular carcinoma' OR 'hepatoma' OR 'liver carcinoma' OR 'liver carcinoma rupture' OR 'liver cell carcinoma' OR 'malignant hepatoma' OR 'primary liver carcinoma' AND ('anabolic agent'/exp OR 'anabolic agent' OR 'anabolic agents' OR 'anabolic drug' OR 'anabolic hormone' OR 'anabolic steroid' OR 'anabolic steroid agent' OR 'anabolic steroids' OR 'anabolizing agent' OR 'anabolizing cream' OR 'anabolizing drug' OR 'anabolizing treatment' OR 'steroid, anabolic' OR 'androgen'/exp OR 'androgen' OR 'androgen sulfate' OR 'androgen sulphate' OR 'androgenic agent' OR 'androgenic hormone' OR 'androgenic steroid' OR 'androgens' OR 'androgens, synthetic').

We have identified 935, 1148, 12 and 3 articles in PubMed, Embase, Scopus and Lilacs, respectively. Last literature research was performed on 27th December, 2017. The three authors searched independently in databases. Only studies, reviews and case reports evaluating the association between androgens and hepatocarcinoma were included with no restrictions in time span or language. Further on, we excluded studies and case reports which patients were receiving therapeutic androgens and collected data only of those reporting androgen intake to improve physical performance.

Six articles fulfilled these inclusion criteria, excluding the duplicates. For general purposes, we included conceptual studies evaluating the link between androgens and HCC.

RESULTS

The review of literature identified 6 case reports linking anabolic androgen steroids uses for enhancing physical performance and hepatocellular carcinoma.

(Table 1) No clinical trials or retrospective studies regarding the subject were found.

DISCUSSION

Historically, the use of anabolic steroids dates back to World War II when they were provided to German soldiers in order to enhance their aggressiveness. Since then, anabolic steroids have become increasingly popular amongst athletes, so much so, that steroid use in both professional and amateur athletics has reached epidemic proportions. In the late 1950s, Ciba Pharmaceuticals introduced methandrostenolone,⁽¹⁴⁻¹⁷⁾ which would become the most popular anabolic drug for athletes. By this time, the era of the steroid athletes was well underway and world records were being shattered and re-shattered with remarkable regularity.⁽¹⁵⁾ Nowadays, this practice is

controlled by specialized agencies, but despite the increased surveillance, it is still a concern in sports.

Estimates of the extent of steroid use among inter-collegiate male athletes range from 2% to 20%.⁽¹⁷⁻²⁰⁾ Two-thirds of AAS abusers start by the age of 16 years⁽¹⁸⁾ and the main reasons for using steroids are to increase strength and size, improve physical appearance, enhance athletic and sexual performance.⁽²¹⁾ In Brazil, the unsupervised use of AAS is a reality and a risk not only for HCC and hepatic adenoma (HCA), but also for fatty liver disease.⁽²²⁾

Table 1. Case reports of hepatocellular carcinoma after long term anabolic androgen steroids use for performance enhancement in healthy subjects

Age	Sex	Androgen, Duration	Patient characteristics	Alfa-fetoprotein	Pathology and management	Outcomes	References
26y	M	Four years taking one or more androgens: methandrostenolone, oxandrolone, stanozolol, nandrolonedecanoate, and methenolone.	Bodybuilder This patient also had a cholangio carcinoma	375ng/mL	Pleural and liver biopsies were performed. Patient refused treatment.	Near total liver replacement by tumor and pleural, pulmonary and intraabdominal metastases. Died 4 months after diagnosis.	Overly et al, 1984. ⁽⁸⁾
37y	M	Five years taking, firstly, methandrostenolone and, after, oxymetholone.	Athlete	NA	Liver biopsy followed by tumor resection. Tumor with 1.8 Kg.	NA	Goldman B, 1985. ⁽⁹⁾
35y	M	Two years taking one or more androgens: testosterone, stanozolol, nandrolonedecanoate	Bodybuilder	Normal	Right hemi-hepatectomy for a tumor with 70 x 90 mm.	NA	Gorayski et al, 2008. ⁽¹⁰⁾
37y	M	Five years taking one or more androgens: Testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, testosterone decanoate, trenbolone acetate, 5alpha-androstenediol, boldenone and methandioldipropionate, 17alpha-Methyl-5alpha-androstano[3,2-c]pyrazole-17beta-ol, 17beta-hydroxy-17alpha-methyl-2-oxa-5alpha-androstane-3-one, oxymetholone or methandienone.	Bodybuilder	Normal	Partial hepatectomy for a tumor with 60 x 60 x 50 mm.	After a follow-up period of 27 months there were no recurrence signs.	Hardt et al, 2012. ⁽¹¹⁾
24y	M	Seven years of testosterone 200mg/week.	Bodybuilder	366 ng/mL	Liver biopsy was performed. The two biggest lesions had 111 x 105 mm (right lobe) and 79 x 72 mm (left lobe).	NA	Kesler et al, 2014. ⁽¹²⁾
29y	M	Six years taking one or more androgens: nandrolone decanoate, sustanon, methandienone, stanozolol.	Bodybuilder	NA	Liver biopsy followed by liver transplantation.	27 months after liver transplantation he is in excellent condition without any signs of metastasis or local recurrence.	Solbach et al, 2015. ⁽¹³⁾

NA: not available

The scarcity of data in the literature linking HCC and AAS in healthy patients for performance improvement might be due to the abnormal development of HCC after AAS usage, underdiagnosis and/or under-reported cases.

Hepatocarcinoma onset after AAS abuse seems to occur at earlier ages than HCC triggered by chronic hepatitis B/C, chronic alcohol consumption and non-alcoholic steatohepatitis (NASH).⁽⁸⁻¹³⁾ HCC outbreak is also time-dependent and long term usage appears to

be required for HCC development and timeframe for onset ranged from two to seven years in the cases reported in this literature review. However, it is important to stress that despite HCC being probably a late complication of continuous AAS use, much other life threatening complications can occur earlier on, so unsupervised AAS usage is a high risk strategy and not recommended to any healthy subjects.⁽⁷⁾ Table 2 describe the main complications of AAS continuous exposure.

Table 2. Adverse events related to anabolic androgen steroids.^(7,22)

Adverse events	
Cardiovascular	Neuropsychiatric
Coronary heart disease	Reduced inhibitory control
Cardiomyopathy	Anxiety
Erythrocytosis	Aggression, violence, impulsive behavior
Hemostasis/coagulation abnormalities	Depression
Dyslipidemia	Hypomania and, occasionally, frank mania
Hypertension	Dependence
Atherosclerosis	Men
Arrhythmia	Hypogonadism
Anatomic remodeling	Testicular atrophy
Infection	Gynecomastia
HIV, hepatitis B and C, MRSA (unsafe needle practices and contaminated products)	Suppression of spermatogenesis
Musculoskeletal	Impaired fertility
Tendon rupture	Acne
Amyotrophic lateral sclerosis	Premature epiphyseal closure
Women	Potential increased risk for prostate cancer
Acne	Renal
Virilization (hirsutism, deepening of voice, clitoromegaly)	Renal insufficiency
Irregular menses	Proteinuria
Hepatic	Nephrotic syndrome
Fatty liver disease	
Cholestasis	
Peliosis hepatis	
Hepatic adenoma	
Hepatocarcinoma	

Hepatocellular carcinoma is more prevalent in men than in women and one of the reasons for this difference could be related to testosterone and androgen receptor (AR) activities.^(2,23,24) Human epidemiological studies have shown that elevated testosterone levels

and the presence of genetic polymorphisms linked to increased androgen activity were significantly associated with a higher risk of HCC in male HBsAg carriers.⁽²⁴⁻²⁶⁾ In rodent HCC models, castration, treatment with anti-androgen agents and modulation of

AR can protect male rodents from tumor development.^(27,28) This evidence suggest that up-regulation of the androgen pathway signaling in male patients is able to accelerate the carcinogenic process in hepatocytes.^(24,27,28)

AAS subtypes seem to induce distinct liver damage; e.g. 17 α -alkylated AAS appear to be hepatotoxic whereas non-alkylated AAS is not. The 17 α -alkyl substitution delays hepatic metabolism of the AAS, rendering it orally bioavailable. The main mechanism responsible for the hepatotoxicity induced by 17 α -alkylated AAS is probably induction of oxidative stress, because it has repeatedly been shown to be associated with this biochemical pathway.⁽²⁹⁾ However, not only oral androgens may induce hepatic neoplasms but also parenteral ones.^(5, 8-13) As several AAS subtypes were used by subjects in case reports, it is difficult to conclude or estimate if a particular AAS is safer than the other.

Since 1965, when the first case report correlating HCC and AAS was published, HCC became a significant concern for patients undergoing long term treatment with androgens, especially those afflicted by hematological diseases as Fanconi's Anemia (FA).⁽⁵⁾ These patients have a strict follow up to their physicians, which include liver imaging to detect any lesions at early stages, allowing effective interventions when needed. Blood markers efficacy is questionable, since alpha-fetoprotein rarely deviates from baseline in early stage disease and liver enzymes may not raise to pathologic levels until death is imminent and unpreventable.^(6,30) The alpha-fetoprotein levels were shown to be high only in two case reports described in this review; the first patient had metastatic disease and the second locally advanced disease. Therefore, these findings are in line with literature^(6,30) and they suggest that this biomarker could be an indicator of disease burden and, for this reason, absent in early stage disease.

When a suspect hepatic focal lesion is identified in a patient undergoing long lasting AAS treatment, its

further characterization is mandatory. The differential diagnosis may be difficult since HCC and hepatic adenoma (HCA), a benign liver tumor, can present similar clinical, radiological, and histological features. One way to differentiate the etiology is that benign lesions can reduce the size or even disappear upon AAS treatment cessation.^(6,30,31) If the nature of the hepatic focal lesion etiology cannot be determined, it is advisable to perform the surgical resection. A major concern is that HCA can undergo malignant transformation, presenting rapid or progressive tumor growth and/or tumor obstruction of the intra-hepatic portal veins. Therefore, close monitoring of HCA lesions is mandatory.⁽¹⁶⁾ Gorayski et al. and Solbach et al. found foci in hepatic lesions devoid of CD34-positive immunostaining, raising the possibility of malignant transformation within a pre-existing adenoma (HCA).^(10,13) The best evidence available in the literature reports a frequency of malignant transformation in about 4.5–9 % of HCA cases.^(32,33) However, if these statistics also hold true for HCC induced by AAS abuse is not known.

Routine abdominal imaging screening in healthy AAS users for performance improvement could be an alternative to detect early stage liver diseases, however, because the abnormal development of such lesions, a better strategy would be focusing on orientation to such population and warning them about the need of medical supervision.

Despite the limited data in the literature and the limitation of a study compiling a small number of cases, we would like to put forth the idea that unsupervised AAS usage is an emerging public health concern, as the population exposed to this practice is usually young, healthy and unaware of the potentially severe adverse events. Furthermore, evidence suggest an association between long term anabolic androgenic steroids abuse for physical performance improvement and hepatocarcinoma.

CONCLUSIONS

Despite the limited evidence, there is some suggestion that hepatocarcinoma may be associated with anabolic-androgenic steroids abuse for performance improvement. AAS must be taken only under specia-

lized supervision and public policies to make high risk populations aware of the risks of AAS misuse and self-administration should be pursued.

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